Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 283 to 305 are pending in the application, with claims 283, 291, and 298 being the independent claims. Since no amendments are being made to the claims, it is believed that a listing of the claims is not required.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Interview with the Examiner

Applicants thank Examiner Eileen O'Hara for the courtesy extended in the personal interview on July 20, 2005 with the undersigned and Applicants' representatives Kenley K. Hoover and Joseph Schuller. The substance of the interview is reflected in the remarks presented herein.

Priority Determination

Applicants thank the Examiner for acknowledging that the soluble TNFR5 polypeptides of the invention are entitled to the priority of provisional application 60/035,496 (the '496 provisional) with respect to the disclosure of a specific and substantial utility. See, *e.g.*, Paper 01182005, page 3, bottom. However, the Examiner now contends that the '496 provisional "does not provide an enabling disclosure of how to use the soluble receptor." (*Id.*, pages 3-4; emphasis added.) In particular, the Examiner has taken the position that while the '496 provisional teaches the use of soluble TNFR5 polypeptides in the treatment of specific diseases and disorders, the '496

application allegedly does not teach which of the disclosed diseases or disorders are mediated by TRAIL. The Examiner contends that in the absence of this teaching, the '496 provisional "did not provide support for which disease or condition could be treated with the soluble receptor." *Id.* Page 4. Accordingly, Applicants have been denied the benefit of the '496 provisional, and the effective priority date has been maintained as the August 7, 1997 filing date of provisional 60/054,885. As a result of this determination, the claims have been rejected under 35 U.S.C. § 102(e) over U.S. Patent Publication No. 2002/0161202. Applicants respectfully disagree and traverse the rejection on the basis that the pending claims are entitled to the priority date of the '496 provisional.

It is well established that an applicant is not required to set forth the mechanisms through which the invention functions, nor is the applicant required to even know how or why an invention works. *See e.g.*, Newman v. Quigg, 11 U.S.P.Q.2d 1340, 1345 (Fed. Cir. 1989); Diamond Rubber Co. v. Consolidated Rubber Tire Co., 220 U.S. 428, 435-36, 55 L. Ed. 527, 31 S. Ct. 444 (1911); Fromson v. Advance Offset Plate Inc., 720 F.2d 1565, 1570, 219 U.S.P.Q. (BNA) 1137, 1140 (Fed.Cir. 1983). Accordingly, the assertion that soluble TNFR5 polypeptides are useful to inhibit apoptosis in the treatment of certain diseases must be considered at face value, regardless of whether the inventors also taught the mechanism of action underlying their assertion. Furthermore, the M.P.E.P. states that

> [i]f multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.

See M.P.E.P. 2164.01(c): "How to Use the Claimed Invention"; emphasis added. Applicants respectfully submit that the instant office action provides neither explanation nor evidence to support the priority determination.

The '496 application asserts that TNFR5 polypeptides "may be employed . . . to treat infectious disease including HIV infection." See '496 provisional at page 7, lines 16-17. At page 51, lines 12-13, the priority document states that "[d]iseases associated with increased apoptosis include AIDS." The '496 specification further teaches that "a method for treating HIV^+ individuals is provided which involves administering an antagonist[1] of the present invention to reduce selective killing of CD4 T-lymphocytes." *Id.*, page 56, lines 14-16. In addition, the '496 specification discloses, through citation of Badley, A.D. *et al.*, *J. Virol. 70*:199-206 (1996) (submitted in the accompanying IDS as document NPL1), a routine assay by which such antagonists could be tested for their ability to prevent HIV-induced apoptosis or T cells. Thus, the '496 provisional teaches a specific and substantial use for soluble TNFR5 polypeptides, and further teaches how to use soluble TNFR5 polypeptides.

There is no evidence on record to support the Examiner's assertion that one of skill in the art, upon reading this disclosure in the '496 provisional, would not know how to use the TNFR5 polypeptides of the invention. The rejection merely states that "[a]poptosis can be caused by many ligands in the TNF family," and that the diseases disclosed in the '496 provisional "are mediated by different ligands." Paper 01182005, pages 3-4. Applicants respectfully submit that these cursory comments fail to acknowledge the substantial body of scientific literature demonstrating the important role

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[1] "Antagonist can include soluble forms of TNFR and monoclonal antibodies directed against the TNFR polypeptide." '496 provisional at page 51, lines 24-26.

of apoptosis in the pathogenesis of infectious disease, and more specifically, the central role of TRAIL-induced apoptosis in the pathogenesis of HIV infection.

For example, Miura and colleagues described the "critical contribution" of TRAIL in the death of grafted $CD4^+$ human lymphocytes in a mouse model of HIV infection. *See* Miura *et al.*, *J. Exp. Med. 193(5)*:651-9 (2001); submitted in the accompanying IDS as document NPL4. These authors report that apoptotic $CD4^+$ cells were frequently found in association with TRAIL-expressing T cells. *See, e.g., id.*, page 655, Figure 2. The authors further found that blocking TRAIL binding with an anti-TRAIL monoclonal antibody was able to inhibit apoptosis in the spleens of HIV infected mice. *See, e.g., id.*, page 656, Figure 3. Based on these observations, the authors suggest that "a similar mechanism may be operative in the pathogenesis of AIDS." *Id.*, page 655, right column. The authors conclude that "TRAIL-mediated apoptosis is the major mechanism of human $CD4^+$ T cell destruction" in the spleens of HIV infected mice, indicating that "TRAIL may be a significant target for preventing the progression of AIDS." These results are supported by experiments on primary cell isolates from HIV-infected humans, demonstrating the involvement of TRAIL in HIV-associated T cell apoptosis. *See, e.g.*, Jeremias *et al.*, *Eur. J. Immunol. 28*:143-152 (1998); submitted in the accompanying IDS as document NPL3. In a recent review, Miura and Koyanagi (*Rev. Med. Virol. 15*:169-178 (2005); submitted in the accompanying IDS as document NPL5) reiterate that "TRAIL seems to be one of the most significant molecules in HIV infection" and state that "[a] novel immune-based therapy for modulating the apoptosis in HIV infection is awaited." *See id.*, page 175. Thus, because of the central role of TRAIL in HIV infection, the teachings of the '496 provisional fully enable the use of

TNFR5 polypeptides to inhibit apoptosis associated with HIV infection, even without disclosing the mechanism by which the TNFR5 polypeptides accomplish this goal.

Even beyond HIV infection, it is clear from the literature that TRAIL contributes to apoptosis in a wide array of infectious diseases. For example, TRAIL-mediated apoptosis contributes to the pathogenesis of measles infection (Okada *et al.*, *Arch. Virol. 145*:905-920 (2000)), hepatitis B (Han *et al.*, *World J. Gastroenterol. 8*(6):1077-1080 (2002)), herpesvirus (Secchiero *et al.*, *Blood 98*(8):2474-2481 (2001)), and respiratory syncytial virus infection (Roe *et al.*, *Clin. Exp. Immunol. 137*:139-145 (2004)) (submitted in the accompanying IDS as documents NPL6, NPL2, NPL8, and NPL7, respectively). Thus, the literature supports the broader assertion that TNFR5 polypeptides are useful to treat infectious diseases. Accordingly, the '496 provisional is enabled for the use of TNFR5 polypeptides to treat not only HIV infection, but infectious diseases generally.

In summary, the '496 provisional teaches that TNFR5 polypeptides are useful in the treatment of infectious disease, including HIV, and further teaches one of ordinary skill in the art how to use such peptides, for example, to prevent or reduce selective killing of HIV-infected CD4 T-lymphocytes. This use of TNFR5 polypeptides of the invention is corroborated by scientific reports published after the filing of the '496 provisional that clearly demonstrate the fundamental role of TRAIL in the pathogenesis of infection, and particularly in the progression of HIV infection. One basis for the outstanding rejection appears to be the allegation that the '496 provisional fails to disclose the mechanism by which the TNFR5 polypeptides accomplish the disclosed uses. However, the case law is clear that disclosing how an invention works is not necessary to enable an invention. Accordingly, unless the Examiner can provide "an

explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use," as instructed by M.P.E.P. § 2164.01(c) (emphasis added), it is respectfully requested that the instant claims be accorded the benefit of the '496 provisional, and that the 102(e) rejection be reconsidered and withdrawn.

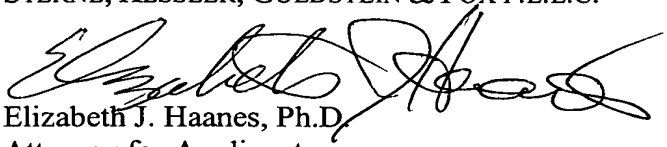
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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